REMARKS

Claims 24, 32, 33, 40, 43 and 45 stand rejected under 35 U.S.C. § 102(a) for purportedly being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) for purportedly being obvious over, WO 98/50079 to Hammond et al.

In addition, claims 24-30 and 35-39 stand rejected under 35 § 103(a) for purportedly being unpatentable over Hammond et al., in view of U. S. Patent No. 5,858,351 to Podsakoff et al.

Applicants respectfully disagree with the Examiner's contention that claims 24, 32, 33, 40, 43 and 45 are anticipated, or in the alternative made obvious, by Hammond et al.. The Examiner asserts that Hammond et al. pages 68-71 (the claims) support her opinion that Hammond et al. teaches treating a patient with congestive heart failure by delivering an AAV vector expressing FGF or VEGF to said patient via direct intracoronary injection of said AAV vector into coronary artery in an amount of AAV virus of 10^6-10^{14} particles. The Examiner contends that if the patient is 60kg then the amount of AAV injected is 17-1.7 x 10^9 particle /g or $1.7x10^3$ to $1.7x\ 10^7$ particles/g body weight. However, the Examiner suppositions are not supported by Hammond. Only a single claim, claim 28 on page 69, recites rAAV:

28. The method of claim 26, wherein the viral particle is a replication –defective adeno-associated virus (AAV).

Claim 28 depends on claim 26, which depends on claim 25, which in turn depends on claim 1. Claims 28, 26 and 25 specify the virus vector that is recited in claim 1, but claims 28, 26 and 25 fail to introduce any other limitations into claim 1. Thus the claim 28 incorporating the language of claim 1 and the intervening claims 25, 26 and 28, would recite:

28. A method for treating a patient suffering from congestive heart failure, comprising delivering a rAAV vector to the heart of said patient, said

rAAV vector comprising a gene encoding an angiogenic protein or peptide operably liked to a promoter for expression of the gene.

Hammond's claim 1 broadly describes a method but does not describe the particular method recited in applicants' claims e.g., delivery via the coronary artery or coronary sinus, or the amount of virus or the stable and efficient transduction of at least 10% of the cardiomyocytes for at least four weeks. Applicant's claim 24 on which claims 32, 33, 40, 43 and 45 depend, recites

24. A method for stable and efficient transformation of cardiomyocytes which comprises:

infusing a recombinant adeno-associated virus (rAAV) vector into a coronary artery or a coronary sinus of an animal in an amount of about $1x10^5$ to about $1x10^9$ infectious units (IU) AAV per gram body weight and for a time sufficient to stably and efficiently transduce cardiomyocytes perfused through said artery or said sinus, wherein said AAV vector comprises at least one nucleic acid molecule operably linked to a control region, said nucleic acid molecule encoding an angiogenic protein wherein at least 10% of cardiomyocytes are transduced and wherein transformation is stable for at least 4 weeks (emphasis added).

None of Hammond's claims 1, 25, 26 or 28 specify infusing a recombinant adeno-associated virus (rAAV) vector into a coronary artery or a coronary sinus.

None of Hammond's claims 1, 25, 26 and 28 recited the amount of rAAV vector that is administered to the patient.

None of Hammond's claims 1, 25, 26 or 28 specify that the rAAV is infused for a time sufficient to stably and efficiently transduce cardiomyocytes.

None of claims 1, 25, 26 or 28 disclose that the nucleic acid molecule encodes an angiogenic protein.

All of the foregoing features are recited in applicant's claim 24 and yet they are missing in Hammonds' claim 28, the only claim that recites rAAV and thus missing from Hammond's pages 68-71.

A proper rejection under 35 U.S.C. 102 requires that a single reference disclose each and every limitation recited in the claims 24, 32, 33, 40, 43 and 45. Pages 68-71 fail to disclose not just one limitation, but fail to disclose multiple limitations that are recited in applicants' claims. As such Hammond fails to anticipate the invention as claimed.

In addition, Examiner states

> "If a patient's average body weight is 60kg, i.e., 6000gm, the amount of AAV virus injected to each patient is 17-1.7 x 10^9 particle /g or $1.7x10^3$ to $1.7x\ 10^7$ particles/g body weight. The range of the AAV virus administered in the present invention falls within the range of the AAV virus taught by Hammond." (Page 3, last paragraph).

The Examiner has based this calculation upon a teaching that Hammond does not provide. As discussed above, Hammond does not disclose administering any specific amount of rAAV to a patient. Thus Hammond does not teach administering any amount of rAAV to a patient based on the patient's weight.

In view of the foregoing it is clear Hammond does not anticipate the invention as claimed. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 102.

The Examiner also states that it is

> "a natural tendency to have an increase in transduced cells over a period of time after the initial transduction process." Office Action, page 4.

Applicants respectfully disagree and directs the Examiner's attention to experimental data by Kaplitt et al. *Ann. Thorac. Surg* 1996; 62:1669-76, which clearly contradicts the Examiner's statements and teaches away from applicant's

invention. Kaplitt states

> "Pigs sacrificed 2 months and 6 months after infusion demonstrated positive cells.... The number of positive cells seen at 2 months after infusion appears to have decreased to approximately 25% of the number seen at 3 days after infusion. By 6 months the number of cells appears to have stabilized and was roughly equivalent to the number of immunoreactive cells observed at 2 months after infusion." (Emphasis added.)
>
> Kaplitt, paragraph spanning pages 1672 and 1673.

In addition, Kaplitt states that only 0.2% of cells are transduced by the rAAV when infused through the coronary artery.

> "Because the titre of the virus used was approximately 5 x 10^7 units/ml and 1ml was infused into each subject, the efficiency of gene transfer is estimated to be roughly 0.2% assuming that these data account for all potential positive cells and that each positive cell represents gene transfer by 1 vector particle."
>
> Kaplitt page 1672, right col.

While Hammond may recite rAAV vectors in a laundry list of other vectors for delivery to the heart, Kaplitt provides experimental data that teaches away from the use of rAAV to efficiently and stably transduce cardiomyocytes. Hammond does nothing to contradict the experimental data presented in Kaplitt. Hammond does not present any data that demonstrates the transduction frequency obtained with rAAV. Therefore one of skill in the art have no reason to expect that stable and efficient transformation of cardiomyocytes could be achieved by infusing a recombinant adeno-associated virus (rAAV) vector into a coronary artery or a coronary sinus of an animal in an amount of about $1x10^5$ to about $1x10^9$ infectious units (IU) AAV per gram body weight. The Examiner's contention that there is "a natural tendency to have an increase in transduced cells over a period of time after the initial transduction process" Office Action, page 4" is refuted by Kaplitt's experimental data, which teaches rAAV does not spread to stably and efficiently transduce cardiomyocytes.

Thus, based on the knowledge in the art and despite Hammond's reference to rAAV in a laundry list of vectors, one of skill in the art would not be motivated by Hammond to infuse rAAV via a coronary artery or coronary sinus to stably and efficiently transduce cardiomyocytes. Nor would one of skill in the expect rAAV to deliver such results. As such Hammond does not anticipate or render obvious applicants' method as claimed and applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 102 and 103.

Claims 24-30 and 35-39 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over Hammond et al. in view of U.S. Patent No. 5,858,351 (Podsakoff). Applicants respectfully disagree.

Kaplitt demonstrates that directly injecting rAAV into the left ventricle led to positive expression of a marker gene but "local to the injection site, with minimal spread" (page 1672, left col.). As discussed supra, Kaplitt also demonstrates that infusing rAAV into the coronary artery does not stably and efficiently transduce cardiomyocytes and in fact the number of transduced cells after infusion declines with time. Podsakoff demonstrates that directly injecting (not infusing via a coronary artery or sinus) rAAV-LacZ into heart ventricles results in 50% transduction of cardiomyocytes at the point of injection. While Hammond may list rAAV as a vector that may be used in his method, the results of Kaplitt and Podsakoff suggest that the efficiency of AAV transduction of cardiomyocytes is very different depending on whether the rAAV is administered by direct injection (Podsakoff, Kaplitt) or by infusion into a coronary artery (Kaplitt). Thus one of skill in the art wishing to achieve stable and efficient transduction of cardiomyocytes, wherein stable and efficient transduction at least 10% of the cardiomyocytes are transduced and the AAV is present in the transduced cardiomyocytes for at least 4 weeks would not be motivated by Podsakoff in combination with Hammond to infuse AAV through the coronary artery or coronary sinus. Furthermore, one of skill in the art would not expect that such infusion would result in an efficient transduction of at least 10% of the cardiomyocytes in the heart.

In view of the foregoing remarks and amendments to the claims, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. BSX 234 US1/10408799 from which the undersigned is authorized to draw.

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Respectfully submitted,

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